

REMARKS/ARGUMENTS

Enclosed is a Revocation and Appointment of Power of Attorney for this application revoking all previous powers of attorney and appointing attorneys and agents of Sheridan Ross P.C. to prosecute this application. This Revocation and Appointment of Power of Attorney is executed on behalf of APBI Holdings, LLC. An Assignment from the original assignee, Eli Lilly and Company to APBI Holdings, LLC was submitted for recordation on May 10, 2004. A copy of the Recordation Form Cover Sheet and Assignment are enclosed for the convenience of the Examiner.

Applicant wishes to thank Examiner Travers for the courtesy extended to Nadine Chien, Joe Kentoffio and the undersigned on May 20, 2004 in a personal interview. During the interview, the prior art rejection under 35 U.S.C. § 103 in view of Houck, Baldwin et al., Lane, Lee et al., and Livni et al. was discussed, along with possible claim amendments and arguments to overcome it.

The above-identified patent application has been reviewed in light of the Examiner's Action mailed December 3, 2003 (Paper No. 11). Claims 19-28, 31, 32 and 34-55 were pending. Claims 19-28, 31-36 and 43-50 have been cancelled without intending to abandon or to dedicate to the public any patentable subject matter. Accordingly, following entry of the foregoing amendments, Claims 37-42 and 51-54 will be pending. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of the claims are respectfully requested.

Applicant notes that the action mailed December 3, 2003 only included initialed 1449 forms from the information disclosure statement submitted on May 23, 2003, and not the 1449 forms from the information disclosure statements filed June 20, 2002 or April 24, 2003. The Examiner is requested to provide initialed copies of these latter two 1449 forms with the next Action.

The amendments to claims 37, 40 and 51-54 find support in the specification (WO 01/17521) at p. 19, ll. 20-25.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner objected to the specification under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention and thereby failing to provide an enabling disclosure. Specifically, the Examiner argues that

the specification does not set forth the criteria that defines compounds having SSRI activity that are useful for practicing the invention as claimed or to ascertain those compounds without undue experimentation. On the basis of this objection, the Examiner rejected Claims 26-28 under 35 U.S.C. § 112, first paragraph. With this Amendment, Applicant has cancelled Claims 26-28 directed to “rapid-onset selective serotonin reuptake inhibitors.” In view of the foregoing, Applicant submits that the Examiner’s rejection under 35 U.S.C. § 112, first paragraph, is moot.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 26-27 under 35 U.S.C. § 102(b) as being anticipated by Lee et al. (J. Clinical Psychopharmacology 16(5):379-82 (1996)). Applicant has cancelled Claims 26-27, and therefore, the Examiner’s rejection of Claims 26-27 under 35 U.S.C. § 102(b), is moot.

Claim Rejections Under 35 U.S.C. § 103

a. The Examiner’s Rejection.

The Examiner has rejected Claims 26-28, 34-42 and 51-54 under 35 U.S.C. § 103(a) as being obvious over:

1. Houck (Psychopharmacology Bulletin, 34(2):225-27 (1998)),
2. Baldwin et al. (Reviews in Contemporary Pharmacotherapy, 6(6):315-25 (1995)),
3. Lane (Journal of Psychopharmacology, 11(1):72-82 (1997)), and
4. Lee et al. (J. Clinical Psychopharmacology 16(5):379-82 (1996)) in view of
5. Livni et al. (Nuclear Medicine and Biology 21(4):669-75 (1994)).

Houck reports the testing of the SSRI fluvoxamine for the simultaneous treatment of anxiety and depression and teaches the side effect of delayed ejaculation as well as nausea, insomnia and nervousness.

Baldwin et al. reviews the use of citalopram, an atypical antidepressant having a structure unrelated to other known SSRIs and more closely related to tricyclic antidepressants, for acute episodes of depression. From the references reviewed, Baldwin et al. report that adverse effects of citalopram include nausea, dry mouth, somnolence, increased sweating, tremor, diarrhea and ejaculation failure (itself a sexual dysfunction).

Lane reviews 92 references with respect to sexual dysfunction related to SSRI use and reports that SSRIs are “clearly associated with delayed ejaculation, inability to ejaculate and absent or delayed orgasm.” Additionally, Lane concludes that “the effects of SSRIs on sexual functioning are clearly dose-related and may vary amongst the group due to their relative effects on the serotonin and dopamine systems and the extent to which plasma levels of these drugs accumulate in the body over time.”

Lee et al. report the results of a clinical trial of fluoxetine to treat premature ejaculation. The authors conclude that their data “suggest that serotonergic antidepressants may be effective in treating rapid ejaculation in men and underlie the need to carry out a double-blind, placebo-controlled trial to confirm these results.”

Livni et al. disclose biodistribution data for a radiolabeled isomer of dapoxetine in rats and a preliminary PET study in a Rhesus monkey using the same isomer. Their results showed a peak concentration in the rat lung at five minutes and displaceable binding in the cerebral cortex and subcortical gray matter. From these results, the authors conclude that it is possible to make the radiolabeled isomer of dapoxetine, and once prepared, it may be useful for *in vivo* evaluation of serotonin re-uptake mechanisms.

Given the information disclosed in these references, the Examiner argues that it would have been obvious to one of skill in the art, absent information, such as unexpected benefits, to the contrary, that any SSRI compound could be used to treat premature ejaculation with a reasonable expectation of therapeutic success. Applicant respectfully disagrees.

b. No *Prima Facie* Case of Obviousness Established.

From prior to the time of filing the present application to the present, there has existed considerable uncertainty in the pharmaceutical arts and the pharmacological literature regarding the use of compounds possessing SSRI activity for the treatment of sexual dysfunction. As described by Baldwin et al. and reviewed by Lane, compounds having SSRI activity are associated with numerous side effects including sexual dysfunction and these effects vary depending on the individual compound, the dose, the distribution of effects between the serotonin and dopaminergic systems, and the plasma levels achieved over time after steady state pharmacokinetics are achieved.

Indeed, further examples of this unpredictability are seen in reports from Mos et al. (European Neuropsychopharmacology, 9:123-35 (1999)) (submitted in the IDS dated 6/20/02) and Kennedy et al. (J. Clinical Psychiatry, 61(4):276-81, abstract, (2000)) (submitted herewith in supplemental information disclosure statement). With studies specifically designed to elucidate the effects of antidepressants on sexual dysfunction and specifically, premature ejaculation, Mos et al. and Kennedy show that the SSRIs differentially affect sexual behavior, sexual dysfunction and premature ejaculation in male subjects.

Kennedy et al. found sertraline- and paroxetine-induced sexual dysfunction in 30% to 70% of the subjects treated but a decreased level of drug-induced sexual dysfunction in instances of favorable drug response. These results varied depending on gender, drug type and pretreatment levels. Mos et al. reviewed the effects of clomipramine, fluvoxamine, fluoxetine, sertraline and paroxetine on premature ejaculation in male rats and showed that paroxetine and fluoxetine markedly and sertraline moderately, inhibited ejaculation latency whereas fluvoxamine did not inhibit this parameter.

As noted by Mos et al., these studies have been extended to human subjects and the results are reported in research articles by Waldinger et al. in the Journal of Clinical Psychopharmacology [18(4):274-81 (1998) (submitted in the IDS dated 6/20/02) and 23(5):467-70, abstract, (2003) (submitted herewith in supplemental information disclosure statement)]. In these reports, Waldinger et al. showed that paroxetine, fluoxetine and sertraline inhibited ejaculation to different extents while fluvoxamine and mirtazapine did not, and that these effects varied depending on the patient's history of the condition. Thus, Waldinger et al. has shown that beginning in 1998 and continuing to the present, the effect of individual SSRI antidepressant compounds on premature ejaculation was not and is not predictable. Thus, contrary to the assertion of the Examiner, the mere fact that dapoxetine displays SSRI activity and a subset of other SSRI antidepressants have been associated with delayed ejaculation would not lead one of skill in the art to have a reasonable expectation of success that dapoxetine would successfully treat premature ejaculation. In fact, the recognition of variability, including no inhibition, in treating premature ejaculation is evidence contrary to an obviousness determination.

At best, the references cited by the Examiner would have made it “obvious to try” a formulation of dapoxetine in the treatment of premature ejaculation in order to produce the presently claimed invention. The Federal Circuit has provided clear direction with respect to arguments based on an “obvious to try” theory. The court has held that an “obvious to try” situation exists when a general disclosure may pique a scientist’s curiosity, such that further investigation might be done as the result of a disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 14 USPQ 2d 1741, 1743 (Fed.Cir. 1990). The court held, however, that “obvious to try” is not to be equated with obviousness under 35 U.S.C. §103. See Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ 2d 1923, 1928 (Fed.Cir. 1990).

In addition, while South African Patent Application No. 930694 (submitted in the IDS dated June 20, 2002) discloses dapoxetine, along with fluoxetine/lovan, duloxetine, amersergide, 228729 and zatosetron, and identifies the potential use of these compounds for treatment of hundreds of conditions spanning eight pages of single-spaced type, including conditions in such disparate areas as tobacco withdrawal, premenstrual conditions, weight loss, memory loss, circadian rhythm disorders, fatigability, sexual disorders (including premature ejaculation), psychoses, nonspecific complaints, and so on, this disclosure is so broad and general as to not effectively disclose the use of dapoxetine for premature ejaculation. Even if this South African application is construed to effectively disclose the use of dapoxetine for premature ejaculation, there is no disclosure or suggestion of the use of dapoxetine on an as-needed basis or the characteristic that it is effective in the absence of priming doses.

For the foregoing reasons, Applicant respectfully submits that because none of Houck, Baldwin et al., Lane, Lee et al., and Livni et al., alone or in combination, provide sufficient suggestions or teachings to direct one of ordinary skill in the art to make the presently claimed invention, the Examiner should withdraw the rejections under 35 U.S.C. §103 predicated upon this combination of references.

c. Even If Prima Facie Case Made, It Is Overcome By Showing Of Unexpected Results.

In further support of Applicant's position that the claimed use of dapoxetine to treat or manage premature ejaculation in a human male is non-obvious, it is important to note that the claims recite the administration of dapoxetine on an as-needed basis and that the administration is effective in the absence of priming doses (an initial period of chronic dosing). Other compounds have been investigated or suggested for the treatment of premature ejaculation. Table 1 below summarizes certain references that were submitted in Information Disclosure Statements dated June 20, 2002, April 24, 2003 and May 30, 2003.

Table 1

Reference	Compound	Comments
McMahon, <i>J. Urology</i> 159:1935-38, June 1998	Sertraline	"This study demonstrates that chronic treatment for premature ejaculation prolongs the ejaculatory interval within 1 to 2 weeks." p. 1937, col. 2
McMahon, <i>J. Urology</i> 159:1935-38, June 1998	Paroxetine	"[P]aroxetine administered on a daily basis produces significantly better ejaculatory control in significantly more patients than does 'on-demand' paroxetine. However, 'on-demand' use of paroxetine appears more efficacious after initial chronic dosing." p. 244, col. 2
McMahon, <i>J. Urology</i> 161:1826-1830, June 1999	paroxetine	"Paroxetine as needed appeared to be more efficacious after initial chronic dosing" p. 1829, col. 1
Haensel, <i>J. Clin Psychopharm.</i> 18(1):72-77, 1998	fluoxetine	daily dosing for four weeks, with suggestion of further study for as-needed dosing
Haensel, <i>J. Urology</i> 156:1310-15, 1996	clomipramine	"Subjects self-administered the capsule . . . 12 to 24 hours before anticipated sexual activity." p. 1311, col. 1

While the sertraline reference (McMahon, *J. Urology* 159:1935-38, June 1998) does not disclose as-needed dosing, it states that a prolonged ejaculatory interval is achieved after 1-2 weeks of *chronic* dosing. The two paroxetine references (McMahon, *J. Urology* 161:1826-1830, June 1999; McMahon, *J. Urology* 159:1935-38, June 1998) disclose as-needed dosing of paroxetine, but conclude that chronic dosing or as-needed dosing after an initial priming period is more effective than as-needed dosing. The fluoxetine reference (Haensel, *J. Clin Psychopharm.* 18(1):72-77, 1998) only discloses chronic dosing, but states that further study is needed to evaluate as-needed dosing. The

clomipramine reference discloses “as-needed” dosing, but the administration is 12-24 hours prior to sexual activity. In addition, it is well recognized in the art that clomipramine is a tricyclic antidepressant and not a SSRI antidepressant, even though the Haensel reference also identifies that clomipramine is recognized as a serotonin re-uptake inhibitor and the compound has activity at the serotonin receptors. The class of tricyclic antidepressants is distinguished from the class of SSRI antidepressants based on their chemical structure and their primary pharmacology characteristics.

As a review of these references shows, while researchers have investigated the use of other SSRIs on an as-needed basis for treatment of premature ejaculation, they teach or suggest the use of priming doses for as-needed dosing to be effective. In contrast, as claimed, dapoxetine is useful for the treatment of premature ejaculation on an as-needed basis and the administration is effective in the absence of priming doses. The study described at pp. 33-41 of the present application was designed to measure ejaculation latency upon delivery of either 20 mg or 40 mg of dapoxetine, 1 to 3 hours prior to sexual intercourse. Patients were asked to attempt intercourse at least 4 times over a 4 week period. Dosing was random and on an as-needed basis depending upon the sexual activity of the patient. No priming period was required in the study. The results indicate that prn dosing of dapoxetine is effective for treating premature ejaculation and that dapoxetine is effective in treating premature ejaculation without a priming dose. (p. 36, l. 18 through p. 41) Indeed, an increase in ejaculation latency was seen after a single dose of dapoxetine. (p. 38, ll. 8-15; Table 12) The increase in ejaculatory latency (EL) in the 20 mg dose over placebo shown in Table 12 is statistically significant (p-value of 0.015) even at the strictest p-value cutoff of p-value < 0.05. The 40 mg single dose increased the EL compared to placebo, but was not statistically significant. The increase in EL in the combined 20 mg and 40 mg doses over placebo is statistically significant (p-value of 0.038) even at the strictest p-value cutoff of p-value < 0.05.

Taken together, the significant and unexpected advantage provided by the claimed invention is that dapoxetine is useful for the treatment of premature ejaculation when used on an as-needed basis in the absence of priming doses, and this advantage is not obvious based on the teachings in the prior art.

d. Rejection of Claims 38-42 and 51-54.

With particular regard to Claims 38-42 and 51-54 reciting specific doses and administration frequencies, the Examiner argues that Livni et al. provides dosage guidance to one of skill in the art to practice the invention as presently claimed. As noted above however, Livni et al. teach the administration of a radiolabeled isomer of dapoxetine to rats followed by detection of the drug in the lung and brain. These results lead the authors to suggest the use of dapoxetine for *in vivo* evaluation of serotonin re-uptake mechanisms. Livni et al., however, only teach tissue distribution of dapoxetine. They do not teach or suggest any suitable dose of dapoxetine for use in either rats or humans. Therefore, Applicant submits that there is no suggestion or motivation in the references rendering the currently claimed dosages of dapoxetine on an as-needed basis obvious to one of skill in the art and respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Applicant is submitting herewith a supplemental information disclosure statement disclosing for submission of the Kennedy and Waldinger references discussed above. In addition, Applicant is submitting Hamilton, *J. Chromatography* 612: 253-261 1993 which discloses a column-switching HPLC method for the determination of dapoxetine and its metabolites.

Based upon the foregoing, Applicant believes that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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